Cell Metabolism
Previews

# Transgenerational Inheritance of Longevity: Epigenetic Mysteries Abound

Shelley L. Berger[1,2,3,*]
[1]Department of Cell and Developmental Biology
[2]Department of Biology
[3]Department of Genetics
1057 BRB, 421 Curie Boulevard, University of Pennsylvania, Philadelphia, PA 19104, USA
*Correspondence: bergers@upenn.edu
DOI 10.1016/j.cmet.2011.12.012

**Transgenerational inheritance of epigenetic characteristics in plants has been reported, whereas nongenetic persistence of complex phenotypes in animals is controversial. A recent report by Anne Brunet and colleagues describes a fascinating example of persistence across generations of extended life span in worm and explores whether epigenetic mechanisms account for the longevity.**

Major questions in the field of epigenetics are whether chromatin states persist through, first, mitotic cell division and, second, meiotic germ cell generation, in both cases to provide memory of the epigenome. The mitotic memory issue is relevant to cell type differentiation during development of multicellular organisms and to loss of differentiation in human disease states such as cancer, as well as to tissue regenerative medicine and the difficulties inherent in erasing or profoundly altering cell identity. The second question, of meiotic memory through germ cells to embryos, while similar in principle, is more provocative, since this could perpetuate nongenetic inheritance across generations. A recent report in *Nature* by Anne Brunet and colleagues unveils a fascinating example of transgenerational inheritance, extending life span in the worm *C. elegans* and potentially regulated by an epigenetic state (Greer et al., 2011).

As background, it is important to understand certain theoretical and practical considerations regarding epigenetic memory. The key theoretical issue is the mechanism(s) underlying cell recollection of identity through cell division, as well as through gametogenesis and early embryogenesis, i.e., whether the molecules that transmit memory consist of DNA-bound transcription factors, long noncoding RNAs, bona fide chromatin-regulatory enzymes, specialized histones, or some combination thereof (Berger et al., 2009). The practical consideration is that many epigenetic regulators are enzymes, enabling discovery of small molecule modulators; such therapeutics are already in the clinic or in aggressive pharmaceutical development and thus have huge potential impact on human health (Rodríguez-Paredes and Esteller, 2011).

There is little doubt that epigenetic memory exists through mitosis; this phenomenon was initially recognized through genetic analysis of development in complex model organisms (Ringrose and Paro, 2004). However, the question of transgenerational memory via chromatin epigenetic states is far more controversial, since it challenges conventional dogma about genetic inheritance. Indeed, previous observations of transgenerational inheritance in animals have been largely anecdotal or epidemiological (Daxinger and Whitelaw, 2010); the evolution of this emerging field requires both molecular experimentation and manipulation.

A number of recent studies have found a chromatin basis for setting life span, including chromatin posttranslational modifications such as reversible histone acetylation. Sirtuins have long been known to have a role in longevity, and although these enzymes have many cellular substrates, histones indeed appear to be key age-relevant acetylated substrates in yeast *S. cerevisiae* and in mouse, functioning at telomeres (Dang et al., 2009; Michishita et al., 2008). Further, histone methylation also contributes to setting life span, as shown in *C. elegans*, in that deletion of the Set2 methylase enzyme or other protein components of the H3 Lys4 (H3 K4) methylase complex extends life span (Greer et al., 2010) (Figure 1A). Thus, there appears to be chromatin regulation of aging through organismal life span involving relaxation of chromatin, which may be deleterious to genomic integrity and lead to aberrant gene expression. Hence, life span is extended by reduction of certain histone modifications (Dang et al., 2009; Greer et al., 2010) or via increased expression of histones themselves (Feser et al., 2010).

Interestingly, Brunet and colleagues now show that deletion of the same worm histone H3 K4 methylase Set2 leads to transgenerational inheritance of life span extension in wild-type offspring (Greer et al., 2011). The authors designed an experimental protocol to avoid maternal effects that might be transmitted to offspring—often a question in transgenerational inheritance studies (Daxinger and Whitelaw, 2010)—by testing offspring from the F3 to F5 generations (Figure 1B). In brief, *set-2*-deficient mutants with extended life span were mated to *SET-2* wild-type worms to yield a heterozygous F1 generation, which was then mated to produce either genetically wild-type or genetically mutant offspring. The authors showed that, remarkably, wild-type offspring in generations F3 and F4 showed the same extended life span as the *set2−/−* offspring (Figure 1B), thereby demonstrating transgenerational inheritance of extended life span in worms.

Although this is a fascinating observation, whether the explanation is truly due to altered chromatin remains to be investigated, since the study does not demonstrate a persistent chromatin effect. That is, an obvious mechanism

would be reduced H3 K4 methylation in the F3 and F4 generations in spite of wild-type *SET-2*; however, the authors tested genome-wide methylation in the long-lived but wild-type offspring, but found no lowering of H3 K4 methylation by global western analysis. This does not rule out possible localized reduction in methylation, for example, at specific genes that might regulate longevity. To indirectly test this hypothesis, the authors performed genome-wide RNA expression microarray analysis. Although the authors detected certain restricted gene expression similarities of the F3 and F4 transgenerational offspring to the actual mutant, the overall transcriptional picture unexpectedly showed expression clustering more similar to the actual wild-type expression spectrum than to the actual mutant expression spectrum. The authors also pointed out that certain specific GO categories that regulate metabolism are altered like the actual mutant; thus, modest changes at a few genes may lead to persistent longevity in the F3 and F4 generations. To address whether this is a direct or indirect effect, it will be important to explore whether H3 K4 methylation is reduced at these genes in the wild-type offspring.

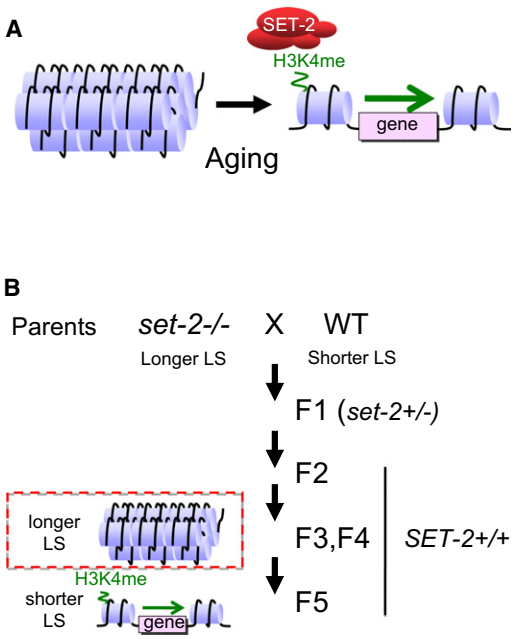


**Figure 1. Transgenerational Inheritance of Longevity**
(A) Aging may lead to decompaction of chromatin, resulting in inappropriate gene expression. In the worm *C. elegans*, deletion of the H3 K4 methylase, SET-2, extends life span.
(B) Transgenerational inheritance of extended life span (LS) in the worm *C. elegans* results from parental deletion of *SET-2* (*set2−/−*) and transmittal to wild-type F3 and F4 generations. Shorter life span is resumed in the wild-type F5 generation.

Another intriguing observation is that the extended life span abruptly returns to normal length in the F5 generation (Figure 1B) without passing through any intermediate longevity state. The authors show an F5 RNA expression microarray with levels similar to the true *SET-2* wild-type, but since the F3 and F4 transcription results are not clearly like *set-2* mutant, the interpretation of these findings remains ambiguous. Moreover, since no altered chromatin state was detected in the F3 and F4 wild-type-but-extended offspring, at present the chromatin state in the F5 generation has yet to be determined. One possibility is that, since there is no transitional partial state, a threshold effect may exist, which would support the idea that there are only a few genes critical to life span extension, and, once the methylation level increases to a certain level in the F5, the life span is no longer extended.

The study also reports that several other longevity genes, including deletion of a few chromatin modulators of transcription that extend life span (e.g., the H3 K9 methylase and H3 K27 demethylases) (Greer et al., 2010; Carone et al., 2010), fail to show a transgenerational longevity effect. Thus, it is tempting to speculate that K4 methylation plays a key role in transgenerational longevity or that other epigenetic mediators of transgenerational longevity exist and have not yet been tested.

Thus, this report establishes a precedent that longevity can be maintained transgenerationally; however, major challenges remain to show a direct epigenetic basis for the transgenerational inheritance. Taken together with other emerging examples in animals of transgenerational inheritance of complex phenotypes with possible underlying epigenetic mechanisms (Carone et al., 2010), we can anticipate many new studies exploring this fascinating question in the near future.

## REFERENCES

Berger, S.L., Kouzarides, T., Shiekhattar, R., and Shilatifard, A. (2009). Genes Dev. *23*, 781–783.

Carone, B.R., Fauquier, L., Habib, N., Shea, J.M., Hart, C.E., Li, R., Bock, C., Li, C., Gu, H., Zamore, P.D., et al. (2010). Cell *143*, 1084–1096.

Dang, W., Steffen, K.K., Perry, R., Dorsey, J.A., Johnson, F.B., Shilatifard, A., Kaeberlein, M., Kennedy, B.K., and Berger, S.L. (2009). Nature *459*, 802–807.

Daxinger, L., and Whitelaw, E. (2010). Genome Res. *20*, 1623–1628.

Feser, J., Truong, D., Das, C., Carson, J.J., Kieft, J., Harkness, T., and Tyler, J.K. (2010). Mol. Cell *39*, 724–735.

Greer, E.L., Maures, T.J., Hauswirth, A.G., Green, E.M., Leeman, D.S., Maro, G.S., Han, S., Banko, M.R., Gozani, O., and Brunet, A. (2010). Nature *466*, 383–387.

Greer, E.L., Maures, T.J., Ucar, D., Hauswirth, A.G., Mancini, E., Lim, J.P., Benayoun, B.A., Shi, Y., and Brunet, A. (2011). Nature *479*, 365–371.

Michishita, E., McCord, R.A., Berber, E., Kioi, M., Padilla-Nash, H., Damian, M., Cheung, P., Kusumoto, R., Kawahara, T.L., Barrett, J.C., et al. (2008). Nature *452*, 492–496.

Ringrose, L., and Paro, R. (2004). Annu. Rev. Genet. *38*, 413–443.

Rodríguez-Paredes, M., and Esteller, M. (2011). Nat. Med. *17*, 330–339.